

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 September 2003 (12.09.2003)

PCT

(10) International Publication Number
WO 03/074500 A3

(51) International Patent Classification⁷: **C07D 451/04**,
451/14, 401/14, 417/14, 413/14, 207/16, 401/04, 417/04,
413/04, 405/04, 211/58, A61K 31/46, 31/395, 31/497,
31/4545, 31/505, A61P 3/10

[HU/HU]; Szent László u. 158., H-1131 Budapest (HU).
VARGA, Márton [HU/HU]; Batthyány u. 9., H-2120
Dunakeszi (HU).

(21) International Application Number: **PCT/HU03/00017**

(74) Agent: **SANOFI-SYNTHELABO**; c/o György Mihályi
and János Őri, Tó u. 1-5., H-1045 Budapest (HU).

(22) International Filing Date: **4 March 2003 (04.03.2003)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
P 0200849 **6 March 2002 (06.03.2002)** **HU**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (*for all designated States except US*): **SANOFI-SYNTHELABO** [FR/FR]; 174 avenue de France, F-75013
Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ARÁNYI, Péter**
[HU/HU]; Bimbó út. 216/226, H-1026 Budapest (HU).
BALÁZS, László [HU/HU]; Tóth Árpád u. 23/a, H-2131
Göd (HU). **BATA, Imre** [HU/HU]; Frankel Leó út 7.,
H-1027 Budapest (HU). **BÁTORI, Sándor** [HU/HU];
Rákóczi út 268/A, H-1214 Budapest (HU). **BORONKAY,**
Éva [HU/HU]; Cibakháza u. 42., H-1162 Budapest
(HU). **BOVY, Philippe** [FR/FR]; 13, rue du 4 Septembre,
F-75750 Mareil Marly (FR). **KÁNAI, Károly** [HU/HU];
Árpád út 88., H-1042 Budapest (HU). **KAPUI, Zoltán**
[HU/HU]; Etele út 56/a, H-1115 Budapest (HU). **SUSÁN,**
Edit [HU/HU]; Hargita u. 21., H-2120 Dunakeszi (HU).
SZABÓ, Tibor [HU/HU]; Alkotás u. 25., H-1123
Budapest (HU). **NAGY, Lajos, T.** [HU/HU]; István u.
47., H-1078 Budapest (HU). **URBÁN-SZABÓ, Katalin**

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv)) for US only*

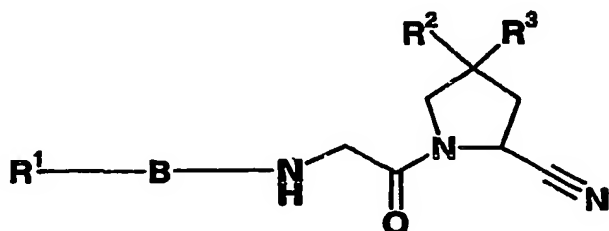
Published:

— *with international search report*

(88) Date of publication of the international search report:
18 December 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **N-AMINOACETYL-PYRROLIDINE-2-CARBONITRILES AND THEIR USE AS DDP-IV INHIBITORS**



(I)

(57) Abstract: The present invention relates to new, potent DPP-IV enzyme inhibitors of the general formula (I), which contain fluorine atoms.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 03/00017

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D451/04 C07D451/14 C07D401/14 C07D417/14 C07D413/14
 C07D207/16 C07D401/04 C07D417/04 C07D413/04 C07D405/04
 C07D211/58 A61K31/46 A61K31/395 A61K31/497 A61K31/4545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 96295 A (NOVARTIS AG ET AL) 20 December 2001 (2001-12-20) the whole document	1-29
X	page 34, example 2kk	23
Y	WO 98 19998 A (NOVARTIS AG) 14 May 1998 (1998-05-14) the whole document	1-29
X	page 12, example 17, page 14, example 66	23
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

15 July 2003

Date of mailing of the international search report

24 07. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 03/00017

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AUGUSTYNS KJL ET AL: "Pyrrolidides: synthesis and structure-activity relationship as inhibitors of dipeptidyl peptidase IV" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 4, 1997, pages 301-309, XP004086653 the whole document, particularly compounds 17b and 18b, and page 303, right-hand column, 2nd paragraph	1-29
P, Y	WO 02 38541 A (TAISHO PHARMACEUTICAL CO., LTD.) 16 May 2002 (2002-05-16) the whole document	1-29
P, X	page 22, formula 9	26, 27

	--- --	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

15 July 2003

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 03/00017

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03 002553 A (SMITHKLINE BEECHAM CORPORATION) 9 January 2003 (2003-01-09) the whole document ---	1-29
X	US 4 001 422 A (DANILEWICZ JC ET AL) 4 January 1977 (1977-01-04) examples 2 and 4 ---	25
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242778 Beilstein Registry Number 6688440 & J. MED. CHEM., vol. 36, no. 23, 1993, pages 3707-3720, ---	25
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242779 Beilstein Registry Number 4298035 & J. MED. CHEM., vol. 34, no. 2, 1991, pages 656-663, ---	25
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242780 Beilstein Registry Number 402384 & J. MED. CHEM., vol. 17, 1974, page 739, 742 ---	25
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242781 Beilstein Registry Number 398284 & J. CHEM. SOC. PERKIN TRANS. 1, 1976, page 938 ---	25
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242782 Beilstein Registry Number 8318995 & TETRAHEDRON LETT., vol. 40, no. 37, 1999, pages 6745-6748, ---	25

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 03/00017

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242783 Beilstein Registry Number 145822 & YAKUGAKU ZASSHI, vol. 71, 1951, page 1053, 1057	25
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242784 Beilstein Registry Number 3609211 & J. HETEROCYCL. CHEM., vol. 19, 1982, pages 485-488,	23
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242785 Beilstein Registry Number 8413665 & ARCH. PHARM., vol. 332, no. 11, 1999, pages 389-398,	23
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242786 Beilstein Registry Number 7996542 & TETRAHEDRON LETT., vol. 39, no. 20, 1998, pages 3121-3124,	23
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242787 Beilstein Registry Number 204710 & CHEM. BER., vol. 74, 1941, page 1661	23
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242788 Beilstein Registry Number 8616397 & J. MED. CHEM., vol. 43, no. 11, 2000, pages 2087-2092,	23

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 03/00017

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 156 433 A (JANSSEN PHARMACEUTICAL N.V.) 2 October 1985 (1985-10-02) example 40 ---	23
X	WO 99 65895 A (SANOFI-SYNTHELABO) 23 December 1999 (1999-12-23) examples 7 and 8 ---	23, 25
P, Y	WO 02 30890 A (TANABE SEIYAKU CO., LTD.) 18 April 2002 (2002-04-18) the whole document P, X page 90, compounds 7-1, 7-3 and 7-7 ---	1-23, 25, 29
P, X	WO 02 51836 A (KYOWA HAKKO KGYO CO., LTD.) 4 July 2002 (2002-07-04) page 23, intermediate for compound 208 ---	23
P, X	WO 03 000250 A (FERRING BV) 3 January 2003 (2003-01-03) example 1D ---	26
P, X	WO 03 002531 A (SMITHKLINE BEECHAM CORPORATION) 9 January 2003 (2003-01-09) Intermediate examples 1E and 2C -----	26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 03/00017

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 23, 25 (both partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 23, 25 (both partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claims 23 and 25. So many documents were retrieved that it is impossible to determine which parts of these claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of said claims.

The search and the report for said claims can only be considered as complete for compounds wherein R1 has the meanings recited in claims 8-12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-23, 25, 29

N-substituted 1-aminoacetyl-2-cyano-pyrrolidines, their use and preparation, and amines

2. Claims: 24, 26-28

Pyrrolidines

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU 03/00017

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0196295	A	20-12-2001	AU 1359702 A CA 2411778 A1 WO 0196295 A2 EP 1296974 A2	24-12-2001 20-12-2001 20-12-2001 02-04-2003
WO 9819998	A	14-05-1998	AU 726186 B2 AU 5318498 A BR 9714130 A CN 1236361 A CZ 9901615 A3 WO 9819998 A2 EP 0937040 A2 HU 0000323 A2 JP 3217380 B2 JP 2000511559 T KR 2000053081 A NO 992028 A NZ 335146 A PL 332777 A1 RU 2180901 C2 SK 60899 A3 TR 9901004 T2 TW 492957 B ZA 9709985 A	02-11-2000 29-05-1998 29-02-2000 24-11-1999 11-08-1999 14-05-1998 25-08-1999 28-08-2000 09-10-2001 05-09-2000 25-08-2000 28-04-1999 29-11-1999 11-10-1999 27-03-2002 10-04-2000 21-07-1999 01-07-2002 07-05-1998
WO 0238541	A	16-05-2002	AU 1274502 A EE 200300175 A WO 0238541 A1	21-05-2002 16-06-2003 16-05-2002
WO 03002553	A	09-01-2003	WO 03002530 A2 WO 03002553 A2 WO 03002531 A2	09-01-2003 09-01-2003 09-01-2003
US 4001422	A	04-01-1977	GB 1460389 A AR 216046 A1 AR 214049 A1 AR 213407 A1 AR 214050 A1 AR 207895 A1 AR 212447 A1 AR 215882 A1 AT 344184 B AT 453077 A AU 8317475 A BG 27086 A3 BG 27744 A3 BG 27745 A3 CA 1060445 A1 CH 611616 A5 CH 608803 A5 DD 119046 A5 DE 2530894 A1 DK 337175 A ,B, FI 752104 A ,B, FR 2279406 A1 HK 61879 A IE 41838 B1 IL 47625 A	06-01-1977 30-11-1979 30-04-1979 31-01-1979 30-04-1979 08-11-1976 14-07-1978 15-11-1979 10-07-1978 15-11-1977 20-01-1977 15-08-1979 12-12-1979 12-12-1979 14-08-1979 15-06-1979 31-01-1979 05-04-1976 05-02-1976 26-01-1976 26-01-1976 20-02-1976 07-09-1979 09-04-1980 30-01-1981

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU 03/00017

Patent document cited in search report		Publication date	Patent family member(s)	Publication date		
US 4001422	A		JP 1036278 C	26-02-1981		
		JP 51036469 A	27-03-1976			
		JP 55027062 B	17-07-1980			
		KE 2988 A	28-09-1979			
		LU 73072 A1	24-03-1977			
		MY 10880 A	31-12-1980			
		NL 7508824 A , B,	27-01-1976			
		PH 14190 A	26-03-1981			
		RO 69296 A1	30-08-1981			
		RO 71841 A1	15-08-1980			
		RO 71840 A1	09-09-1982			
		SE 420921 B	09-11-1981			
		SE 7508101 A	26-01-1976			
		YU 124181 A1	30-04-1983			
		YU 124281 A1	30-04-1983			
		YU 184275 A1	27-04-1983			
		AT 344185 B	10-07-1978			
		AT 453177 A	15-11-1977			
		AT 344186 B	10-07-1978			
		AT 453277 A	15-11-1977			
		AT 344178 B	10-07-1978			
		AT 525275 A	15-11-1977			
		BE 831654 A1	23-01-1975			
		CS 192549 B2	31-08-1979			
		CS 192534 B2	31-08-1979			
		EP 156433	A	02-10-1985	US 5001125 A	19-03-1991
				AT 61050 T	15-03-1991	
AU 576563 B2	01-09-1988					
AU 4034885 A	03-10-1985					
BG 43690 A3	15-07-1988					
CA 1238321 A1	21-06-1988					
CS 8501952 A3	18-11-1992					
DE 3581819 D1	04-04-1991					
DK 134185 A , B,	27-09-1985					
EP 0156433 A2	02-10-1985					
ES 8606289 A1	01-10-1986					
FI 851177 A , B,	27-09-1985					
GR 850714 A1	14-06-1985					
HU 37614 A2	23-01-1986					
IL 74707 A	31-05-1988					
JP 60226862 A	12-11-1985					
KR 8701158 B1	13-06-1987					
NO 851167 A , B,	27-09-1985					
NZ 211494 A	30-05-1988					
PH 22495 A	12-09-1988					
PL 252562 A2	03-12-1985					
PT 80157 A , B	01-04-1985					
RO 91197 A1	30-06-1987					
SU 1384198 A3	23-03-1988					
US 5157035 A	20-10-1992					
US 5292738 A	08-03-1994					
ZA 8502235 A	26-11-1986					
ZM 1785 A1	27-03-1986					
ZW 5485 A1	22-10-1986					
WO 9965895	A	23-12-1999	FR 2780057 A1	24-12-1999		
		AT 222250 T	15-08-2002			

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU 03/00017

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9965895	A		AU 4048299 A	05-01-2000
			DE 69902535 D1	19-09-2002
			DE 69902535 T2	10-04-2003
			EP 1087961 A1	04-04-2001
			ES 2183557 T3	16-03-2003
			WO 9965895 A1	23-12-1999
			JP 2002518385 T	25-06-2002
<hr/>				
WO 0230890	A	18-04-2002	AU 9419601 A	22-04-2002
			AU 9419701 A	22-04-2002
			BR 0114436 A	01-07-2003
			CA 2424600 A1	02-04-2003
			CA 2424964 A1	18-04-2002
			EP 1323710 A1	02-07-2003
			EP 1325910 A1	09-07-2003
			WO 0230890 A1	18-04-2002
			WO 0230891 A1	18-04-2002
			JP 2002356471 A	13-12-2002
			JP 2002356472 A	13-12-2002
			NO 20031490 A	02-06-2003
<hr/>				
WO 0251836	A	04-07-2002	WO 02051836 A1	04-07-2002
<hr/>				
WO 03000250	A	03-01-2003	WO 03000250 A1	03-01-2003
<hr/>				
WO 03002531	A	09-01-2003	WO 03002530 A2	09-01-2003
			WO 03002553 A2	09-01-2003
			WO 03002531 A2	09-01-2003
<hr/>				